Serial No.: To Be Assigned

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please replace the paragraph starting on page 9, line 1 with the following:

[Figure 2.] Figures 2A to 2C. C4 Reversed Phase Purification of Heregulin

Please replace the paragraph starting on page 9, line 3 with the following:

[Panel A:] Figure 2A. Pool C from the polyaspartic acid column was applied to a C4 HPLC column (SynChropak RP-4) equilibrated in 0.1% TFA and the proteins eluted with a linear acetonitrile gradient at 0.25%/minute. The absorbance trace for the run numbered C4-17 is shown. One milliliter fractions were collected for assay.

Please replace the paragraph starting on page 9, line 9 with the following:

[Panel B:] Figure 2B. Ten microliter aliquots of the fractions were tested in the HRG2 tyrosine autophosphorylation assay. Levels of phosphotyrosine in the $p185^{HER2}$ protein were quantitated by a specific antiphosphotyrosine antibody and displayed in arbitrary units on the [absissa] abscissa.

Please replace the paragraph starting on page 9, line 15 with the following:

[Panel C:] Figure 2C. Ten microliter fractions were taken and subjected to SDS gel electrophoresis on 4-20% acrylamide gradient gels according to the procedure of Laemmli (Laemmli, U.K., *Nature*, **227**:680-685, 1970). The molecular weights of the standard proteins are indicated to the left of the lane containing the standards. The major peak of tyrosine phosphorylation activity found in fraction 17 was associated with a prominent 45,000 Da band (HRG2-α). Another peak of activity (fraction 40) was associated with a protein of apparent molecular weight of 14,000 Da (HRG2-β).

Please replace the paragraph starting on page 10, line 1 with the following:

[Figure 4 depicts] Figures 4A to 4D depict the entire coding DNA nucleotide sequence of the known heregulin 2-α and the deduced amino acid sequence of the cDNA contained in λgt_{10}her16 (Seq. ID Nos 10 and 11). The nucleotides are numbered at the top left of each line and the amino acids written in single letter code are numbered at the bottom left of each line. The nucleotide sequence corresponding to the probe is nucleotides 681-720. The probable transmembrane amino acid domain is amino acids 287-309. The six cysteines of the EGF motif are 226, 234, 240, 254, and 256. The four potential three-amino acid N-linked glycosylation sites are 164-166, 170-172, 208-210 and 437-439. The serine-threonine potential O-glycosylation sites are 209-221. Serine-glycine dipeptide potential glycosaminoglycan addition sites are amino acids 42-43, 64-65 and 151-152.

Please replace the paragraph starting on page 10, line 24 with the following:

Sequences of several EGF-like proteins around the cysteine domain are aligned with the sequence of HRG2-α (SEQ ID Nos. 12-17). The location of the cysteines and the [invarient] invariant glycine and arginine residues at positions 238 and 264 clearly show that HRG2-α is a member of the EGF family. The region of highest amino acid identity of the family members relative to HRG2-α (30-40%)

is found between Cys 236 and Cys 264. The strongest identity (40%) is with the heparin-binding EGF (HB-EGF) species. HRG2-α has a unique 3 amino acid insert between Cys 240 and Cys 254. Potential transmembrane domains are boxed (287-309). Bars indicate the carboxy-terminal sites for EGF and TGF-alpha where proteolytic cleavage detaches the mature growth factors from their transmembrane associated proforms. HB-EGF is heparin binding-epidermal growth factor; EGF is epidermal growth factor; TGF-alpha is transforming growth factor alpha; and schwannoma is the schwannoma-derived growth factor.

Please replace the header on page 85, line 10 with the following:

[Example 6] Example 4

Please replace the header on page 85, line 27 with the following:

[Example 7] Example 5

Please replace the header on page 87, line 1 with the following:

[Example 8] Example 6